## REMARKS

Claims 1-20 are pending in the present application. The Examiner rejects all of the pending claims 1-20.

### *Rejection under the judicially created doctrine of obviousness type double patenting*

The Examiner rejects all of claims 1-20 under the judicially created doctrine of obviousness type double patenting as unpatentable over U.S. Patent Nos. 5,804,370, 6,203,997, and 6,306,614. Applicants submit herewith three properly executed Terminal Disclaimers hereby disclaiming the patent term of any claims that issue from the present application beyond the patent term of the aforementioned patents without addressing the merits of the rejections. The submission of the Terminal Disclaimers is made purely to advance prosecution of the application and secure speedy issuance of a patent.

### *Rejection under 35 U.S.C. §112*

The Examiner rejects claims 1-20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter.

The Examiner rejects claims 1, 4, 8, 10, 15 and 17 as allegedly vague and indefinite for the recitation of "oxidant-producing phagocytic cells." The Examiner contends that it is unclear what these oxidant-producing cells are and that this terminology is not known in the art. Applicants herein change the claim language to further clarify the invention. In accordance with amendments made in response to a similar rejection in Serial No. 09/353,189, now U.S. Patent No. 6,306,614, using language suggested by the Examiner, all of the subject claims have been amended to read "white blood cell," as supported for example, in the paragraph bridging pages 5-6. Applicants believe that the term is adequately defined and well known to those of skill in the

art. Withdrawal of the rejection is respectfully requested.

The Examiner rejects claims 7, 13 and 15 as allegedly vague and indefinite because of the recitation "analyte is indicative of the extent of infection or sepsis." The Examiner questions whether the infection is viral or bacterial as well as how many analytes are involved. Applicants remind the Examiner that the open ended claim language "comprising" lends meaning to the claim so that there may be one or more analytes present. Applicants further intend the claim language to encompass both bacterial and viral infections and do not wish to be limited in these regards. Applicants submit that the language that the Examiner finds offensive is clear on its face. However, in the interest of further clarifying the claims, Applicants change the language to "analyte concentration is elevated during infection or sepsis." No issue of new matter arises by way of this amendment as support may be found throughout the specification and inherently in the claim language as filed.

The Examiner rejects claims 1, 8 and 15 because of the recitation of "the amount" indicating that there is insufficient antecedent basis. Applicants herein correct the antecedent basis by changing "the" to "a."

The Examiner further rejects claims 1, 8 and 15 because of the recitation of "the presence" indicating that there is insufficient antecedent basis. Applicants herein remove the offending language as this recitation is not required to define the invention and distinguish the claimed invention from the prior art.

The Examiner rejects claims 8 and 15 as allegedly being vague and indefinite for the recitation of "that produced by a maximal amount of immunocomplexes." The Examiner questions what constitutes the maximal amount of immunocomplexes and how does one know that amount. Applicants respectfully traverse the rejection. With regard to "that produced by a maximal amount of immunocomplexes," Applicants submit that the maximal amount of immunocomplexes is defined in the paragraph bridging pages 13-14. Applicants further point out

that the maximal stimulation of chemiluminescence in whole blood occurs when antigen-antibody complementarity is optimal for the formation of macromolecular crosslinked immunocomplexes or aggregates. Applicants contend that a skilled artisan would be able to determine an amount of the anti-analyte antibody for a particular set of assay conditions based upon the source of the sample and the source of the oxidant-producing white cells (among other factors) and an amount of analyte that in combination with the same amount of anti-analyte antibody would elicit the maximal stimulation of oxidant production. The skilled artisan would establish appropriate antigen-antibody concentrations to yield such optimal complementarity resulting in maximal immunocomplex formation through basic titration methods using various dilutions of analyte and anti-analyte antibodies. All could be accomplished routinely and without undue experimentation. In light of the foregoing, Applicant respectfully requests withdrawal of the rejection.

The Examiner states that claim 6, 12 and 18 are indefinite in the recitation of the abbreviations "fMLP". Applicants herein amend the subject claims to expressly set forth the meaning of the term as N-formyl-met-leu-phe. Support for the amended claim can be found in the specification on page 9, second paragraph, among other places.

The Examiner rejects claim 12 as reciting broad limitations such as "said analyte measured is indicative of the sepsis" and questions whether the infection is a bacterial, viral or a parasitic infection. Moreover, the Examiner has posed the question as to how many analytes are involved in each one of these sepsis. Applicants respectfully traverse the Examiner's rejections. Applicants wish to point out that the method of the invention is not directed to any one particular analyte, but may be applied to any of a variety of analytes, such as, but not limited to, those related to infection and sepsis that are included in the instant application. Applicants submit that one of skill in the art desirous of diagnosing infection or sepsis using the instantly claimed method would select an appropriate analyte for a specific type of infection, such as viral, bacterial or fungal products, if the object of the test is a specific microbial product, or one will select an inflammatory mediator which is produced generally in response to microbial products

as the analyte for a general test. In light of the foregoing, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112.

***Rejection under 35 U.S.C. §102***

The Examiner rejects claims 1-20 under 35 U.S.C. 102(b) as being anticipated by Romaschin *et al.* (WO 94/29728). Applicant respectfully traverses the rejection and notes that the instant application is a Continuation-in-Part of Application Serial Number 09/585,582 which is a Continuation-in-Part of Application Serial Number 09/353,189, now U.S. Patent No. 6,306,614; which is a Continuation-in-Part of Serial No. 08/552,145, filed November 2, 1995; now U.S. Patent No. 5,804,370; which is a Continuation-in-Part of Serial No. 08/516,204, filed August 17, 1995, abandoned; which is a Continuation-in-Part of Serial No. 08/257,627, filed June 8, 1994, now abandoned, which is a national stage entry of PCT/CA94/00325 filed June 8, 1994, and which claims priority of Canadian Application Serial No. 2,097,952, filed June 8, 1993. The specification as filed includes the information since entry into the United States national stage. Applicants herein amend the specification to include the foreign priority claim under 35 U.S.C. 119(a). Since the subject matter disclosed in the instant application claims priority to and is fully supported by an earlier application (Serial No. 08/257,627, filed June 8, 1994), filed prior to the publication of WO 94/29728, Applicants contend that the rejection under 35 U.S.C. 102(b) is incorrect. The cited reference is not prior art against the instant application. In light of this, withdrawal of the rejection is courteously requested.

***Rejection under 35 U.S.C. §103***

The Examiner rejects claims 1-20 under 35 U.S.C. §103(a) as being unpatentable over De Baetselier (U.S. patent No. 4,737,455) in view of Winkelhake *et al.* (Journal of Infectious Diseases, Vol. 165, pp. 26-33, 1992). The Examiner says that De Baetselier teaches the property of phagocyte cells to show chemiluminescence when activated by certain chemical or immunological agents used for qualitative or quantitative measurement of analytes in biological fluids. Allegedly, a variety of analytes such as endotoxins, lymphokines, membrane specific

antibodies and their antigens, toxic substances and others can be analyzed by this method. Moreover, a chemiluminescent substrate such as luminol or lucigenin is added to intensify the chemiluminescence. De Baetselier use hybrid phagocyte cells instead of normal phagocyte cells. The Examiner admits that the methods of De Baetselier differ from those of the present invention in using hybrid phagocyte cells and in using a different control sample, *i.e.* one without the fluid to be analzyed rather than one without the antibodies against the target antigen. However, the Examiner contends that it would have been obvious to one of ordinary skill in the art to omdify the method of DeBaetselier by using the claimed normal phagocyte cells and to modify the control sample by deleting reagent antibody instead of sample fluid in order to control for the variability of the normal phagocyte cells. Additionally, the Examiner says that De Baetselier teaches that the amount of chemiluminescence is proportional to the amount of stimulator/analyte/antigen present. The Examiner further admits that De Baetselier do not teach detecting gram negative bacteria such as *E. coli, Klebsiella pneumoniae* or *Pseudomonas aeruginosa.* However, the Examiner contends that it was routine to detect gram negative bacteria for diagnosing sepsis and infection using antigen-antibody interactions and cites to Winkelhake *et al.* as teaching gram negative bacteria.

The Examiner has not set forth a *prima facie* case of obviousness

Applicants respectfully traverse the rejection. The Examiner fails to set forth a *prima facie* case of obviousness. For a proper *prima facie* case of obviousness based upon multiple references, the references must in combination disclose all elements of the claimed invention. This simply not the case when De Baetselier and Winkelhake et al. are considered in combination.

De Baetselier does not teach or suggest the present invention alone or in combination

De Baetselier do not teach or suggest many facets of the instant invention. The presently claimed method employs a measure of oxidants produced by white blood cells present in a reaction in the determination of the quantity of an analyte from a comparison of the oxidant produced by white blood cells. No standard curve relating direct assay readout to analyte level is

employed as in the prior art, as this would require a standard curve for every test. In contrast, the present invention is based on a highly reproducible relationship between the amount of oxidant produced by white blood cells and the amount of analyte in the sample, as noted on page 20, lines 17-20 and page 21, lines 1-4. Hence, the amount of analyte may be quantitated from this single determination.

Moreover, the methods according to the presently claimed invention may be carried out with white blood cells endogenously present in the sample or from another source or sources, and do not require the addition of hybrid cells as required by the methods of De Baetselier. It is simply unnecessary to add a standardized white cell population in the presently claimed methods. Applicants have discovered that unstandardized endogenous white blood cells are sufficient to provide a quantitative test. Applicants note that the present invention is not limited by the source of white blood cells which may include any combination of those endogenously present in the sample, as well as added cells from another source or, indeed, hybrid cells. However, Applicants reiterate that De Baetselier does not teach or suggest using a single quantification of oxidants rather than a standard curve, regardless of the source of white blood cells, to provide a quantitative readout. Applicants provide methods that make this possible, representing a significant and unobvious advancement over the prior art.

Winkelhake *et al.* do not cure the deficiencies of De Baetselier

The Examiner cites to Winkelhake *et al.* as teaching that gram negative bacteria may be detected using an antigen-antibody interaction and thereby used to diagnose infection and sepsis. Applicants do not dispute the fact that detecting gram negative bacteria is clinically useful. The present invention is not novel and nonobvious over the prior art methods because it may be applied to detecting gram negative bacteria. Rather, the present invention is novel and nonobvious because of the manner in which such detection is performed. Hence, Winkelhake et al. in no way cure the deficiencies of De Baetselier. In light of the above and foregoing, withdrawal of the rejection is respectfully requested.

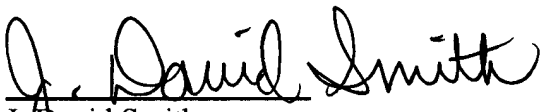
***Fees***

No additional fees are believed necessary in connection with this submission. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

***Conclusion***

Applicants respectfully request entry of the foregoing amendments and remarks. Reconsideration and withdrawal of all of the outstanding rejections is believed in order. Early and favorable action on the claims is earnestly solicited. Should a discussion be helpful in resolving any outstanding issues, the Examiner is invited to telephone the undersigned at (201) 487-5800.

Respectfully submitted,



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